Targeting cancer stem cells in gastric cancer

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Stem Cells

Double capacity

Self renew
Without transforming into specialized cells

Differenciate

Progenitor or transit-amplifying cells

Normal stem cell

Mutations

Cancer stem cell

Mature tissue

Bulk tumor
Cancer Stem Cells

Dysregulation in
- JAK/STAT
- Wnt/beta-cat
- Hedgehog
- NANOG
- Notch
- c-myc

Unregulated cell divisions

Normal stem cell → Mutations → Progenitor or transit-amplifying cells → Mature tissue

Cancer stem cell → Bulk tumor
Cancer stem cells

- Highly Tumorigenic
- Fundamentally responsible for continued malignant growth
- Resistant to chemo and current targeted therapies
- Initiators (seeds) of metastasis
Different populations

Heterogeneous Cancer Cells

Cancer Stem Cells

Cancer Stemness Inhibitor

Cancer cells with stemness

Without stemness
Resistance to treatment

- Cancer stem cells and cancer cells with stemness are resistant to current therapies
- Conventional therapies can induce cancer stemness
- Relapsed cancer, after initial response to current therapies, displays stemness phenotypes
Target cancer stem cells

Cancer stem cell specific therapy → Tumor regression

Conventional cancer therapy

Low ROS levels
MDR activation → Tumor relapse
Target cancer stem cells

• Challenging because:
  • Heterogeneity of the CSC population, not all the same
  • Lack of specific surface markers for mab use
  • Mutations also in CSC, dynamic process
  • STAT 3, dysregulated in many cancer and involved in stemness properties, may be a good candidate
STAT 3 inhibitors

• Targeting STAT3 is challenging:
  • Unstable molecules
  • Poor membrane permeability
  • Poor pharmacokinetic…

• OPB-31121: disease control but no shrinkage, neurotoxic
• OPB-51602: more efficient but not tolerated (Neurotoxic, GI toxicities...)
• AZD9150: efficient in hematology not in solid tumors
**BBI-608 Targets CSCs**

- **BBI-608**
  - First in class
  - Small Molecule
  - Orally administered
  (80 mg capsules)

*Spheres cultured for 1-2 week; treatment of spheres for 24 hours*
BBI-608 Blocks CSC Spherogenesis

DMSO | BBI-608 0.4uM | Imatinib 2mM | Sunitinib 10mM | Erlotinib 10mM

![Images of spheroids for each condition]
BBI-608 Spares Normal Stem Cells

**Myeloid**

**Erythroid**

IC$_{50}$ for cancer stem cells $< 0.5$uM

IC$_{50}$ for normal hematopoietic stem cells $>> 30$uM

<table>
<thead>
<tr>
<th>Cell type</th>
<th>IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer stem cells</td>
<td>100-500</td>
</tr>
<tr>
<td>Hematopoietic stem cells</td>
<td>$&gt;30,000$</td>
</tr>
<tr>
<td>Normal cells</td>
<td>Non toxic</td>
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BBI608 (napabucasin) Directly Inhibits Stat3 - a Key Driver of Cancer Stemness & Immune Evasion Mechanisms

Cancer Stemness
- ↓ Nanog
- ↓ Sox2
- ↓ β-Catenin
- ↓ c-Myc

Immune Evasion Mechanisms
- Immune checkpoint modulation
  - ↓ IDO1 expression
  - ↓ PD-L1 expression
- Immune suppressive microenvironment
  - ↑ MHC class II expression
  - ↑ IL-10 (Th1 response)
  - ↑ Effector T cell infiltrate
BBI-608 Targets STAT3

STAT3

Supershift

DMSO

OSM

100

300

600

608 (nM)

STAT3 / DNA binding
BBI-608 is a first-in-class Cancer Stemness Inhibitor

Effect of BBI-608 Treatment on p-STAT3 and β-catenin Protein Levels in Human PDAC Cell Line (Panc-1). Cells treated with BBI-608 or control were analyzed by immunofluorescence staining using antibodies specific for human p-STAT3 and β-catenin.
Encouraging signs of anti-cancer activity in patients with gastric/GEJ adenocarcinoma are being positively confirmed in additional cohort.
Study Schema

<table>
<thead>
<tr>
<th>Screening</th>
<th>Randomization</th>
<th>Active treatment</th>
<th>Follow up</th>
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- **Screening**
- **Randomization**
- **Active treatment**
  - BBI608 orally, twice daily
  - Paclitaxel 80 mg/m² IV, weekly (three out of every four weeks)
- **Follow up**
  - Interim Analysis (OS): Test for Superiority at 2/3 of required events (380) death
  - Disease Progression based on RECIST or unacceptable toxicity

**Planned sample size:** 700 patients
(350 pts on BBI608 arm and 350 pts on Placebo arm)

**Geographic Locations:** N. America, S. America, Europe, Australia, Asia/Japan

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1If no other therapies are available at the time of disease progression, and the patient has not experienced clinical deterioration, BBI608/Placebo may be continued.